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EXAMINER	
STAPLES, MARK	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
12/29/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/560,236	WINTER ET AL.	
	Examiner	Art Unit	
	MARK STAPLES	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *10 and 13-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11,12 and 25* is/are rejected.

7)☒ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment of claims 1, 4, 5, 7, and 25 in the paper filed on 10/02/2009 is acknowledged.

Claims 1-9, 11, 12, and 25 consonant with the species election of RHODAMINE GREEN™ (5-(6)-carboxyrhodamine) are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections that are Withdrawn

Claim Rejections Withdrawn - 35 USC § 112 Second Paragraph

2. The rejections of claim 7 for containing the trademark/trade names RHODAMINES™, BODIPY™, and ALEXA™ without a corresponding unique chemical name is withdrawn as Applicant has amended the claim to recite unique chemical names corresponding to the dyes of the trademarks.

Claim Rejections Withdrawn - 35 USC § 112 First Paragraph

3. The rejection of claims 1-5, 7-9, 11, 12, and 25 is withdrawn under 35 U.S.C. 112, first paragraph, as containing subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant has amended the claims to overcome this rejection.

Claim Rejections Withdrawn - 35 USC § 103(a)

4. The rejection of claims 9 and 25 under 35 U.S.C. 103(a) as being unpatentable over Rudert et al. (1997) Tyagi et al. (United States Patent No. 6,150,097 issued 2000, previously cited), Weisburg et al. (United States Patent No. 6,110,678 issued 2000, previously cited), and Nunnally et al. (1997, previously cited) is withdrawn. Applicant's arguments with have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

Rejections that are Maintained

Claim Rejections Maintained - 35 USC § 103

5. The rejections of claims 1-6, 8, 9, 11, and 12 under 35 U.S.C. 103(a) as being are maintained. The rejections are provided below. Applicant's arguments filed 10/02/2009 have been fully considered but they are not persuasive.

Applicant argues that the Rudert teaches a double end labeled fluorogenic probe which forms a hairpin structure. However the probe taught by Rudert in Figure 3 is not a hairpin structure but a linear probe of the same type as the claimed probe (and without internal complementary regions as claimed). This probe binds to a partial hairpin structure which is the analyte. Furthermore, the probe of Rudert has a thymidine on the 5' end as claimed and a pyrimidine nucleotide spacer on one end as claimed. Thus Rudert teach a probe with key structural components of the claimed probe. Even further, detection occurs by cleaving and release of one the dyes on the 5' end and thus allows detection of the analyte (the hairpin structure). Tyagi teach two identical

fluorescing dyes on the ends of one probe and at least suggest the probes do not need a hairpin structure as the probe so constructed is altered in a detectable fashion. Rudert teach one of these detectable fashions as already stated and where the probe does not have a hairpin structure. Thus it would have been obvious to one of ordinary skill at the time of the claimed invention that a probe with identical fluorescing dyes would have the property of detection as taught by Rudert. Once the fluorophore is cleaved, it can be detected as taught by Rudert. And as taught by Rudert the fluorophores need not be in contact with each other in order to be detected. Rudert teaches pyrimidines on the end of a probe and Weisberg teaches it was well known to place pyrimidines on the ends of probes for capture on a solid phase. Thus from the combine teachings of Rudert and Weisberg, it would have also been obvious to one of ordinary skill at the time of the claimed invention that probes with pyrimidines on the ends. Nunnally teach the elected flourophore and teach it can be substituted for the fluorophores taught by Rudert, Tyagi, and Weisberg. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Rejections Maintained

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-6, 8, 9, 11, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rudert et al. (1997) Tyagi et al. (United States Patent No. 6,150,097 issued 2000, previously cited), Weisburg et al. (United States Patent No. 6,110,678 issued 2000, previously cited), and Nunnally et al. (1997, previously cited).

Regarding claim 1, Rudert teaches probes (entire article) having the general structural formula (I):

5'-M-$(Z)_n$-X_1-X_2-... X_m-$(Z)_n$'-M'-3'

wherein X_1, X_2 ... and X_m are in each case an arbitrary nucleotide or nucleotide analog and in which the sequence X_1- X_2 -... X_m is a probe sequence which is capable of binding to an analyte (see the sequence of the TET-DR control probe and its analyte target which is the Hairpin in Figure 3) and also see the DRB specific probe where m is 18 (see legend to Figure 5) and allowing for Z's as follows

Z is a spacer, in each case independently, pyrimidine nucleotides being thymidine and cytidines of CTTC at the 5' end and thymidine of T at the 3' end,

M and M' are fluorescent labeling groups, where M is a reporter fluorescent dye at the 5' of either 6-FAM, HEX, or TET and M' is the quencher fluorescent TAMRA dye at the 3' end (see the 1st full paragraph of body text on p. 1141 and see the TET-DR control probe in Figure 3),

n and n' are integers with n respectively being 4 which is within the range of from 1 to 15 and also within the range of 3-10 and of 1 which is within the range of from 1 to 15, and

m is an integer corresponding to the length of the probe sequence and wherein $(Z)_n$ does not hybridize with $(Z)_n'$, as neither the TET-DR probe nor the DRB specific probe has complementary ends (see Figures 3 and 5).

Regarding claim 15, Rudert does not specifically teach the species election of RHODAMINE GREEN for M and M'. Further regarding claim 25, Rudert teaches where n is 4 and thus within the range of 1-15, but do not specifically teach where n' is also a pyrimidine.

Regarding claim 1, Tyagi et al. teach that the same fluorescent dye can be used on each of end of probe for a fluorescing and quenching pair (see column 3 lines 45-48). Tyagi et al. teach probes but do not specifically teach where each probe end is a Z which is a pyrimidine nucleotide and wherein $(Z)_n$ does not hybridize with $(Z)_n'$. Further

regarding claim 1, Tyagi et al. do not specifically teach the species election of RHODAMINE GREEN for M and M'.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the probes of Rudert et al. by using the same dye on each end of the probe as suggested by Tyagi et al. with a reasonable expectation of success. The motivation to do so is provided by Tyagi et al. who teach that separation of the same dye as both fluorescing and quenching moieties on ends of a probe alters the absorption spectra in a detectable fashion (see column 3 lines 40-48) and that the separation can be achieved by cleavage of the probe (see column 3 lines 1-32) as also taught by Rudert et al. (see Figure 3 and its legend). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Regarding claims 1, 4, 5, 9, 11, and 12, Weisburg et al. teach probes where Z_n is a repetitious sequence of at least C_5 by teaching C_n, or of at least T_5 by teaching T_n where n is at least about 10 bases (column 8 Lines 36-59). And it is noted that the repetitious sequences of Weisberg et al. do not hybridize with the target sequence but to a synthesized complement which can be on a solid phase (see Figure 4). Weisburg et al. teach that fluorescent moieties well known in the art can be used on probes (column 19 lines 29-34), but do not specifically teach where the fluorescent moiety is RHODAMINE GREEN™ and do not specifically teach the same fluorescent moiety on each end of a probe.

Regarding claim 2, Weisburg et al. teach the further specie election of formula (II) where X is - O-; Y is =O; Y' is -OH; and R is –OH (see Structure 1 in column 13).

Regarding claims 3 and 6, Weisburg et al. teach thymidine 2' deoxynucleotides (see Example 1).

Regarding claims 1, 4, 8, 9, and 12, Nunnally et al. teach fluorescein, as also taught by Tyagi et al. above, and that RHODAMINE GREEN™ may be substituted for fluorescein (see Table 1 and see the 1st full paragraph in the 2nd column on p. 2394). Nunnally et al. teach that the use of fluorescein in probes was well known (see 1st full paragraph on p. 2392).

Rudert et al. in combination with Tyagi et al. teach pyrimidine nucleotides on the ends of a probe and teach identical fluorophores including fluorescein on the ends of the claimed probes. Weisburg et al. teach multiple pyrimidine nucleotides on the ends of probes and fluorescent labels on the ends of these. Nunnally et al. teach that the use of fluorescein was well known and that RHODAMINE GREEN™ (5-(6)-carboxyrhodamine) may be substituted for fluorescein. Because Rudert et al., Tyagi et al., and Weisburg et al. each teach well known fluorophores, it would have been obvious to one skilled in the art to substitute the well known fluorescein of Tyagi et al. as the fluorophore for the well known fluorophores of Weisberg to arrive at the claimed probe, but with fluorescein being the identical fluorophore on each end (instead of RHODAMINE GREEN™). As Nunnally et al. teach RHODAMINE GREEN™ may be

substituted for fluorescein, it would have been obvious to one skilled in the art to substitute RHODAMINE GREEN™ for the fluorescein of Tyagi et al. and Weisberg et al. in the probe of Rudert et al., Tyagi et al., and Weisburg et al. in order to achieve the predictable result of a probe having ends of pyrimidine nucleotide sequences with RHODAMINE GREEN™ at the ends of each of the pyrimidine nucleotide sequences.

New Objections and Rejections Necessitated by Amendment

New Claim Objections

9. Claim 9 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in dependent form. Claims 9 recites the limitation where "M and M' are identical" which is already recited in antecedent claim 1.

New Claim Rejections - 35 USC § 103

10. Claims 7 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rudert (1997, previously cited), Tyagi et al. (United States Patent No. 6,150,097 issued 2000, previously cited), Weisburg et al. (United States Patent No. 6,110,678 issued 2000, previously cited), Nunnally et al. (1997, previously cited), Davies et al. (1996), and Mathias et al. (US Patent no. 6,177,247 issued 2001).

Regarding claims 7 and 25, Rudert teaches probes (entire article) having the general structural formula (I):

5'-M-$(Z)_n$-X_1-X_2-... X_m-$(Z)_n$'-M'-3'

wherein X_1, X_2 ... and X_m are in each case an arbitrary nucleotide or nucleotide analog and in which the sequence X_1- X_2 -... X_m is a probe sequence which is capable of binding to an analyte (see the sequence of the TET-DR control probe and its analyte target which is the Hairpin in Figure 3) and also see the DRB specific probe where m is 18 (see legend to Figure 5) and allowing for Z's as follows

Z is a spacer, in each case independently, pyrimidine nucleotides being thymidine and cytidines of CTTC at the 5' end and thymidine of T at the 3' end,

M and M' are fluorescent labeling groups, where M is a reporter fluorescent dye at the 5' of either 6-FAM, HEX, or TET and M' is the quencher fluorescent TAMRA dye at the 3' end (see the 1st full paragraph of body text on p. 1141 and see the TET-DR control probe in Figure 3),

n and n' are integers with n respectively being 4 which is within the range of from 1 to 15 and also within the range of 3-10 and of 1 which is within the range of from 1 to 15, and

m is an integer corresponding to the length of the probe sequence and wherein $(Z)_n$ does not hybridize with $(Z)_n$', as neither the TET-DR probe nor the DRB specific probe has complementary ends (see Figures 3 and 5).

Regarding claims 7 and 25, Rudert does not specifically teach the species election of RHODAMINE GREEN for M and M'. Further regarding claim 25, Rudert teaches where n is 4 and thus within the range of 3-10, but do not specifically teach where n' is also within the range of 3-10.

Regarding claims 7 and 25, Tyagi et al. oligonucleotide probes and teach that the same fluorescent dye can be used on each of end of probe which are detectable (see column 3 lines 45-48). Tyagi et al. teach probes but do not specifically teach where each probe end is a Z which is a pyrimidine nucleotide and wherein $(Z)_n$ does not hybridize with $(Z)_n$'. Further regarding claims 7 and 25, Tyagi et al. do not specifically teach the species election of RHODAMINE GREEN (5-(6)-carboxyrhodamine) for M and M'.

Regarding claims 7 and 25, Davis et al. teach DNA probes which contain one to fluorescein labels at different positions including the 3' and 5 ' ends of the probes (entire articles, especially the Abstract). Davis et al. further teach a spacer which can be ethylene glycol gave higher signals and reduced fluorescein self-quenching (Abstract) inprobes with two fluoresceins, but do not specifically teach where the spacer is a pyrimidine nucleotide. Davis et al. do not specifically teach the species election of RHODAMINE GREEN (5-(6)-carboxyrhodamine) for M and M'.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the probes of Rudert et al. by using the same dye on each end of the probe as suggested by Tyagi et al. and Davis et al. with a reasonable expectation of success. The motivation to do so is provided by Tyagi et al. who teach that separation of the same dye as both fluorescing and quenching moieties on ends of a probe alters the absorption spectra in a detectable fashion (see column 3 lines 40-48) and that the separation can be achieved by cleavage of the probe (see

column 3 lines 1-32) as also taught by Rudert et al. (see Figure 3 and its legend). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Regarding claims 7 and 25, Mathias et al. teach a probe of 24 base total length and ending in the pyrimidine nucleotide which is thymidine labeled at position 11 with 5-carboxyfluorescein, "N", and teaches the same probe double labeled with the identical fluorophore (See SEQ ID NO: 9 in columns 21, and note the two positions labeled in the probe, each labeled with 5-carboxyfluorescein). Regarding claims 7 and 15, Mathias teaches a probe of 12 base total length and ending in the pyrimidine nucleotide which is thymidine labeled with N,N,N', N' - tetratmethyl-6-carboxyrhodamine, "N" (See SEQ ID NO: 8 in columns 20 and 21); but do not specifically teach the species election of RHODAMINE GREEN (5-(6)-carboxyrhodamine) for M and M'.

Regarding claims 7 and 25, Weisburg et al. teach probes where Z_n is a repetitious sequence of at least C_5 by teaching C_n, or of at least T_5 by teaching T_n where n is at least about 10 bases (column 8 Lines 36-59). And it is noted that the repetitious sequences of Weisberg et al. do not hybridize with the target sequence but to a synthesized complement which can be on a solid phase (see Figure 4). Weisburg et al. teach that fluorescent moieties well known in the art can be used on probes (column 19 lines 29-34); but do not specifically teach the same fluorescent moiety on each end of a probe.

Regarding claims 7 and 25, Nunnally et al. teach fluorescein, as also taught by Tyagi et al. and Davies et al. above, and that RHODAMINE GREEN™ may be substituted for fluorescein (see Table 1 and see the 1st full paragraph in the 2nd column on p. 2394). Nunnally et al. teach that the use of fluorescein in probes was well known (see 1st full paragraph on p. 2392); but do not teach indentical fluorophores on the ends of a probe.

Tyagi et al. teach identical fluorophores including fluorescein on the ends of a probes. Davies et al. also teach identical fluorophores which are fluoresceins on the ends of a probes. Rudert et al. in combination with Tyagi et al. and Davis et al. teach pyrimidine nucleotides on the ends of a probe and teach identical fluorophores including fluorescein on the ends of the claimed probes. Mathias et al. teach probes ending with a fluorescently labeled thymidine and teaches probes with two identical labels. Weisburg et al. teach multiple pyrimidine nucleotides on the ends of probes and fluorescent labels on the ends of these. Nunnally et al. teach that the use of fluorescein was well known and that RHODAMINE GREEN™ (5-(6)-carboxyrhodamine) may be substituted for fluorescein. Because Tyagi et al., Davies et al, Rudert et al., Mathias et al., and Weisburg et al. each teach well known fluorophores, it would have been obvious to one skilled in the art to substitute the well known fluorescein of Tyagi et al. or Davies et al. as the fluorophore for the well known fluorophores of Weisberg to arrive at the claimed probe, but with fluorescein being the identical fluorophore on each end

(instead of RHODAMINE GREEN™). As Nunnally et al. teach RHODAMINE GREEN™ may be substituted for fluorescein, it would have been obvious to one skilled in the art to substitute RHODAMINE GREEN™ for the fluorescein of Tyagi et al. and Weisberg et al. in the probe of Tyagi et al., Davies et al., Rudert et al., and Weisburg et al. in order to achieve the predictable result of a probe having ends of pyrimidine nucleotide sequences with RHODAMINE GREEN™ at the ends of each of the pyrimidine nucleotide sequences. Davies et al. also provide motivation to do so as they teach that fluorescein is a model system for fluorophores (see 3rd paragraph of the text body on p. 702) and teach that system of multiple fluorphores are not difficult to construct for maximal signal:

> "It is not difficult to try several oligonucleotide constructs for a given ligand to identify the most suitable position for fluoresceination that gives a maximal signal upon binding to the target. Similarly, it is also possible to identify a position for a fluorophore in a ligand that gives maximal quenching upon interaction with a target, a feature that may be useful in other diagnostic applications, such as homogeneous detection" (see the 4th and 5th sentences on p. 706).

Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

11. No claim is free of the prior art.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark Staples/
Primary Examiner, Art Unit 1637
December 19, 2009